

REMARKS

This application has been amended in a manner that is believed to place it for allowance at the time of the next Official Action.

Claims 74-100 are pending in the present application. Claims 74-94 have been amended to address several informalities found within the claims. New claims 95-100 have been added. Support for new claims 95-100 may be found in the present specification page 36, lines 1-16; page 36, lines 21-37; page 38, lines 25-38; and page 40, line 10 to page 42, line 7. Claim 1-73 has been cancelled.

Applicant notes with appreciation that the Information Disclosure Statement filed on February 2, 2002 and the amendment filed on January 30, 2004 are acknowledged by the United States Patent and Trademark Office. However, applicant notes that the references cited in Form PTO-1449 have not been initialed. For the Examiner's convenience, a copy of Form PTO-1449 is attached with this amendment. At this time, applicant respectfully requests that the Examiner initial the references that have been considered in the Form PTO-1449 so that the record is clear as to this matter.

In the outstanding Official Action, claim 89 was rejected under 35 USC §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the

invention. Applicant believes the present amendment obviates this rejection.

In imposing the rejection, the Official Action alleged that the term "LHRH" was not clearly defined. However, claim 89 has been amended to recite "luteinizing hormone-releasing factor (LHH)". In addition, applicant provides a definition for "luteinizing hormone-releasing factor" from the Merk Index. As to the term "triptoreline", applicant also encloses the definition for "triptorelin". In view of the definitions from the Merk Index, applicant believes that the terms are definite to one skilled in the art.

Claims 73-76, 80-82, and 86-89 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 18, 17, 14, and 7-10 of U.S. Patent No. 6,120,786. This rejection is respectfully traversed.

As the Examiner is aware, a double patenting rejection of the obvious-type is "analogous to the nonobviousness requirement of 35 U.S.C. 103 with the exception that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwate*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Thus, any analysis employed in an obvious-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination.

Applicant submits that the claimed invention is not obvious in view of the claims of U.S. Patent No. 6,120,786. U.S. Patent No. 6,120,786 is directed to a medicament adapted to be administered parentally. The medicament comprises an active ingredient and has a diameter of from about 0.2 to about 2 mm. The length of the medicament is from about 1 mm to about 5 cm. The medicament has crush strength of at least about 8 killipoise in the longitudinal direction (see independent claim 7).

Thus, the claims of the 6,120,786 patent are directed to a needle-less device for the parental administration of a medicament. The medicament has the shape of one end of a toothpick. It is placed in the bore of a barrel with the barrel having the shape of a nose cone at one end. A plunger is then inserted into the other end of the bore. The plunger forces the medicament through the skin and into a subcutaneous layer of a patient without the need for the penetration of the skin by a needle.

This stands in contrast to the claimed invention which is directed to a solid delayed-release formulation for parental administration comprising a homogenous mixture of an active principle through an invasive device delivering said formulation in a body wherein the active principle is a proteic or peptidic active principle, in a non-dispersed state forming a continuous phase which of at least one part is in direct contact with the exchange surface of the formulation and of the exterior biological

medium, and of a biodegradable biocompatible excipient, in which the quantity of active principle is at least 50% by weight with respect to the total weight of the formulation, having a release profile which is independent of the composition of the excipient, of the molecular weight of the excipient or of the active principle/excipient weight ratio, the release profile being substantially dependent on the total quantity of active principle present in the formulation.

In other words, the claimed formulation is adapted for the implantation or the insertion via a device such as a needle, trocar, or catheter, wherein the formulation is protected during the parental introduction of the implant. In addition, the implant does not require the high crush strength of the medicament claimed in U.S. Patent No. 6,120,786.

In addition, the formulation according to the present invention can be administered into various internal deposit sites which may be corporeal cavities, endotheliae or tissues, wherein the medicament of U.S. Patent No. 6,120,786 is typically inserted just under or in the skin.

Thus, in view of the distinct differences between the claims of the U.S. 6,120,786 patent and the claimed invention, applicant believes that one of ordinary skill in the art would not find the claimed invention obvious in view of the claims of U.S. Patent No. 6,120,786.

Claims 73, 74, 79, 80, 81, 82, 84, 86, 87, 89 and 91 were rejected under 35 USC §102(b) as allegedly being anticipated by KENT et al. 4,675,189. Applicant believes the present amendment obviates this rejection.

Applicant believes that KENT et al. fail to disclose or suggest the claimed invention. KENT et al. disclose a microcapsule composition comprising a core containing a water-soluble hormonally active polypeptide encapsulated in a biodegradable, biocompatible copolymer excipient (see column 1, lines 10-30). In other words, the small cores are encapsulated into an excipient cover. The delivery rate is dependent on the properties of the excipient which surround the small cores. Thus, KENT et al. is directed to an encapsulated microsphere.

The microspheres are not an implantable formulation. An implantable formulation should be able to remain as a solid or semi-solid mass for a substantial period time period and would not be readily dispersed in the organism such as a microsphere. Applicant further believes that the publication fails to provide any teaching or suggestion to modify the disclosed microspheres to obtain a solid delayed-release formulation that can be implanted into a deposit site as set forth in the claimed invention.

As a result, applicant believes KENT et al. fail to anticipate or render obvious the claimed invention.

Claims 75-78, 83, 85, 87, 88 and 90 were rejected under 35 USC §103(a) as allegedly being unpatentable over KENT et al. in view of ORSOLINI et al. 5,445,832.

ORSOLINI et al. disclose a method for manufacturing microspheres whereby the active principle is changed into an insoluble salt; the salt is then suspended in a biodegradable polymeric solution which is then formed into droplets through an emulsion. This leads to microparticles embedded into the excipient with an active principle content of between 5 and 24%. Thus, there is no continuous phase of active principle as in the formulation according to the present invention and this publication is quite comparable to the KENT et al. citation.

As to the rejection of claim 85, applicant could not find any comparison between *in vitro* and *in vivo* release. Rather, ORSOLINI et al. generically state in one of the examples that the release duration can be of about 8 days. There is no teaching directed to a phase of an active principle.

Similar to the KENT et al. publication, the microspheres cannot be defined as an implantable formulation. An implantable formulation should be able to remain as a solid or semi-solid mass during a substantial time and not be able to be readily disposed in an organism as microspheres would.

Thus, in view of the above, applicant believes that ORSOLINI et al. fail to remedy the deficiencies of KENT et al.

As a result, applicant believes that the proposed combination fails to render obvious the claimed invention.

Claims 91-94 were rejected under 35 USC §103(a) as allegedly being unpatentable in view of KENT et al. in view of ORSOLINI et al. and further in view of BOYAN et al. 5,492,697. This rejection is respectfully traversed.

Applicant believes that one of ordinary skill in the art would lack the motivation to combine and modify the teachings of KENT et al., ORSOLINI et al. and BOYAN et al. to obtain the claimed invention.

BOYAN et al. is directed to a biodegradable implant for placement in nonunion bone fractures as a substitute for bone graft material. As disclosed at column 5, lines 40-50, the implant has a honeycomb structure for placement in nonunion bone fractures and is provided as a bone graft. Thus, the structure disclosed by BOYAN et al. is quite distinct from those taught by KENT et al. and ORSOLINI et al. As a result, applicant believes that one of ordinary skill in the art would lack the motivation to combine the teachings of BOYAN et al. with KENT et al. and ORSOLINI et al.

Thus, in view of the above, applicant believes that the proposed combination fails to render obvious the claimed invention.

In view of the present amendment and the foregoing remarks, therefore, applicant believes that the present

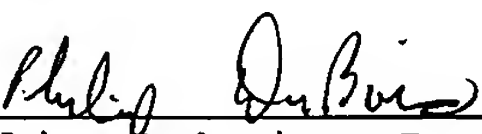
application is in condition for allowance, with claims 94-100, as presented. Allowance and passage to issue on that basis is respectfully requested.

Please charge the fee of \$90 for the five extra claims of any type and \$88 for the extra independent claim added herewith, to Deposit Account No. 25-0120.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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**Appendix:**

The Appendix includes the following items:

- definitions of LHRH and triptorelin at pages 5500 and 9883 of the Merck index 12<sup>th</sup> Ed.
- Form PTO-1449 filed on February 1, 2002

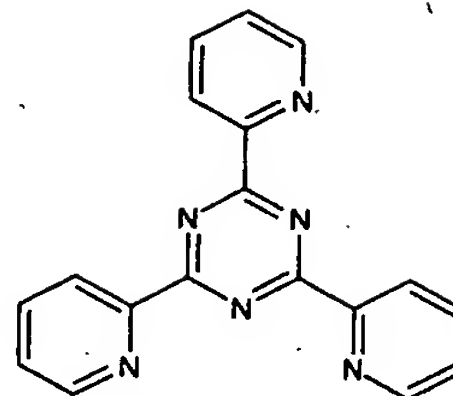
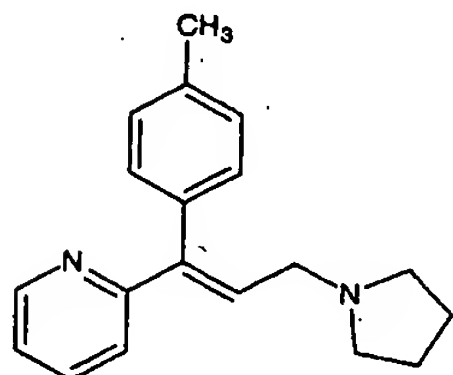




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## Tris(hydroxymethyl)nitromethane

9883



Crystals from light petr, mp 59-61°. uv max (ethanol): 236, 285 nm ( $\epsilon$  15300, 6800).

Hydrochloride monohydrate,  $C_{19}H_{22}N_2 \cdot HCl \cdot H_2O$ , 295C51, Actidil, Actidilon, Pro-Actidil, Pro-Entra, Venen. Crystals from water, mp 116-118°. uv max (ethanol): 235, 283 nm ( $\epsilon$  15000, 7400). Moderately sol in water, ethanol, methanol.

Oxalate,  $C_{19}H_{22}N_2 \cdot C_2H_2O_4$ , crystals from methanol, dec 173-174°. uv max (ethanol): 233, 283 nm ( $\epsilon$  16200, 8200).

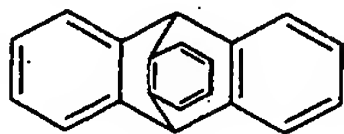
THERAP CAT: Antihistaminic.

**9878. Triptorelin.** 6-D-Tryptophanluteinizing hormone-releasing factor (pig); 6-D-tryptophan-LH-RH; D-trp<sup>6</sup>-LHRH; D-Trp<sup>6</sup>LRH; D-trp<sup>6</sup>-gonadorelin; détryptoréline; AY-25650; Wy-42462; Wy-42422.  $C_{64}H_{82}N_{18}O_{13}$ , mol wt 1311.47. C 58.61%, H 6.30%, N 19.22%, O 15.86%. Synthetic peptide agonist analog of LH-RH, q.v. Prepn: A. V. Schally, D. H. Coy, Ger. pat. 2,625,843; *eidem*, U.S. pat. 4,010,125 (1976, 1977); D. H. Coy *et al.*, *J. Med. Chem.* 19, 423 (1976). Comparison with LH-RH of *in vitro* activity: D. H. Coy *et al.*, *Biochem. Biophys. Res. Commun.* 67, 576 (1975). Pharmacokinetics and metabolism in humans: J. L. Barron *et al.*, *J. Clin. Endocrinol. Metab.* 54, 1169 (1982). HPLC analysis: D. C. Serti *et al.*, *J. Liq. Chromatog.* 4, 1135 (1981). RIA in human serum: M. Mason-Garcia *et al.*, *Proc. Nat. Acad. Sci. USA* 82, 1547 (1985). Clinical trial in prostatic carcinoma: H. Parmar *et al.*, *Lancet* 2, 1201 (1985); for *in vitro* fertilization: A. Hazout *et al.*, *Fertil. Steril.* 59, 596 (1993).

5-oxoPro-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-GlyNH<sub>2</sub>

Fluffy, white solid.  $[\alpha]_D^{25} -58.8^\circ$  ( $c = 0.33$  in acetic acid). Acetate,  $C_{64}H_{82}N_{18}O_{13} \cdot C_2H_4O_2$ , *Decapeptyl*. THERAP CAT: Gonad-stimulating principle; antineoplastic (hormonal).

**9879. Triptycene.** 9,10-Dihydro-9,10-o-benzanthracene.  $C_{20}H_{14}$ , mol wt 254.33. C 94.45%, H 5.55%. Synthesis by three different methods: Bartlett *et al.*, *J. Am. Chem. Soc.* 64, 2649 (1942); Wittig, *Org. Syn.* 39, 75 (1959); Friedman; Logullo, *J. Am. Chem. Soc.* 85, 1549 (1963).



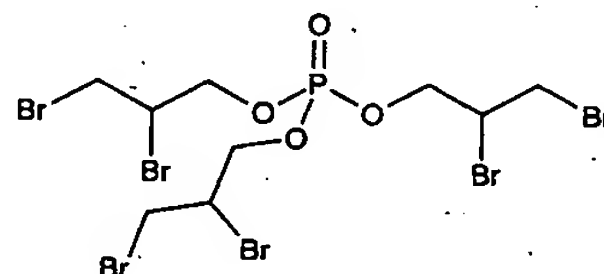
Crystals from cyclohexane or methylcyclohexane, mp 253-254°.

**9880. 2,4,6-Tripyridyl-s-triazine.** 2,4,6-Tri-2-pyridyl-s-triazine; 2,4,6-tripyridyl-1,3,5-triazine; tripyridyltriazine; TPTZ.  $C_{18}H_{12}N_6$ , mol wt 312.33. C 69.22%, H 3.87%, N 26.91%. Synthesis: Case, Kroft, *J. Am. Chem. Soc.* 81, 905 (1959). Preparation: Schaefer, U.S. pat. 3,294,798 (1966 to Am. Cyanamid). Thermal stability data: Johns *et al.*, *J. Chem. Eng. Data* 7, 227 (1962). Review: "2,4,6-Tripyridyl-s-triazine" in Diehl *et al.*, *The Iron Reagents* (The G. Frederick Smith Chem. Co., Columbus, Ohio, 1965) pp 41-56.

Crystals, mp 210-220° (Schaefer); trihydrate from aqueous ethanol, mp 244-245° (Case, Kroft). Reacts with ferrous ions to yield intense violet color over pH range 3.4-5.8. Absorption max  $Fe(TPTZ)_2^{2+}$  (water): 593 nm ( $\epsilon$  22600), Collins *et al.*, *Anal. Chem.* 31, 1862 (1959).

USE: Reagent for the spectrophotometric deterrn of iron.

**9881. Tris-BP.** 2,3-Dibromo-1-propanol phosphate(3:1); phosphoric acid tris(2,3-dibromopropyl) ester; tris(2,3-dibromopropyl) phosphate; Apex 462-5; Flammex AP; Flammex T 23P; Firemaster LV-T 23P; Firemaster T 23P; T 23P; Fyrol HB 32.  $C_9H_{15}Br_3O_4P$ , mol wt 697.61. C 15.50%, H 2.17%, Br 68.72%, O 9.17%, P 4.44%. Prepn: G. E. Walter, I. Hornstein, U.S. pat. 2,574,515 (1951 to Glenn L. Martin Co.); D. E. Overbeek, R. C. Nametz, U.S. pat. 3,046,297 (1962 to Michigan Chem. Co.); R. W. Rimmer, U.S. pat. 3,223,755 (1965 to duPont). Use in flameproofing: W. D. Paist, N. Van Gorder, U.S. pat. 2,662,834 (1953 to Celanese). Mutagenicity studies: M. J. Prival *et al.*, *Science* 195, 76 (1977); A. Nakamura *et al.*, *Mutat. Res.* 66, 373 (1979). Carcinogenicity studies: B. L. Van Duuren *et al.*, *Cancer Res.* 38, 3236 (1978); G. Reznik *et al.*, *J. Nat. Cancer Inst.* 63, 205 (1979). Review of toxicology: F. A. Daniher, *Proc. Symp. Text. Flammability* 4, 126-143 (1976). Review: A. Blum, B. N. Ames, *Science* 195, 17 (1977).



Viscous liquid. LD<sub>50</sub> orally in rats: > 5.0 g/kg (Daniher).

Note: This substance may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 396.

USE: Flame retardant. Formerly used in children's sleepwear.

**9882. Tris(ethylenediamine)cadmium Dihydroxide.** Tris(ethylenediamine)cadmium hydroxide; tri(en)cadmium hydroxide; Cadoxen.  $C_6H_{26}CdN_6O_2$ , mol wt 326.72. C 22.06%, H 8.02%, Cd 34.41%, N 25.72%, O 9.79%.  $[Cd(H_2NCH_2CH_2NH_2)_3](OH)_2$ . Prepared by shaking a given amount of cadmium oxide in 10 times its wt of 30%-aq ethylenediamine soln for 15 minutes and centrifuging; the supernatant liquor is the product: Jayme, Neuschäfer, *Naturwiss.* 44, 62 (1957). The soln contains about 4.5% Cd (w/w) and dissolves about 3% (w/w) cellulose, giving a clear, highly viscous soln.

USE: Solvent for cellulose: Jayme, Ger. pat. 1,079,318 (1960 to E. Merck), C.A. 55, 18107d (1961); solvent for sulfite pulps.

**9883. Tris(hydroxymethyl)nitromethane.** 2-(Hydroxymethyl)-2-nitro-1,3-propanediol; 2-nitro-2-(hydroxymethyl)-1,3-propanediol; trimethylolnitromethane.  $C_3H_7NO_5$ , mol wt 151.12. C 31.79%, H 6.00%, N 9.27%, O 52.94%. Prepn from trioxymethylene and nitromethane: Boileau, *Mém. Poudres* 35, Annexe 7-76 (1953).

FORM PTO-1449 U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICEATTY. DOCKET NO.  
0512-1009-1SERIAL NO.  
New**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**  
(Use several sheets if necessary)APPLICANT  
Roland CHERIF CHEIKH

37 CFR 1.98(b)

FILING DATE  
February 1, 2001GROUP  
Unknown**U.S. PATENT DOCUMENTS**

EXAMINER INITIAL		PATENT NUMBER	ISSUE DATE	PATENTEE	CLASS	SUB CLASS	FILING DATE IF APPROPRIATE
	AA	5,573,542	11-96	Stevens			
	AB	5,543,156	8-96	Roorda et al.			
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

**FOREIGN PATENT OR PUBLISHED FOREIGN PATENT APPLICATION**

		DOCUMENT NO.	PUBL. DATE	COUNTRY OR PATENT OFFICE	CLASS	SUB CLASS	TRANSLATION YES NO
	AJ	0 529 675	3-93	EUROPE			
	AK	0 596 161	5-94	EUROPE			
	AL	522 404	3-31	GERMANY			
	AM	84/00304	2-84	PCT			
	AN						

**OTHER DOCUMENTS (Including Author, Title, Date, Relevant Pages, Place of Publication)**

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**EXAMINER****DATE CONSIDERED****EXAMINER: Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.**